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ON THE AETIOLOGY OF LEUKOEMIA.

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A study of the enormous literature dealing with leukoemic states, not only convinces us that all research has been futile in intimating ourselves with the "causae proximae sive determinantes" of these obscure diseases, but also that the lines of inquiry have been the same since Hughes Bennett described his case of "suppuration of the blood," and Virchow his case of "leukoemia" or 'white blood.'

These two papers, contain, with little change our modern conception of the unknown causative factors which initiate these mysterious conditions. It may be said, that Bennett, - who in his first paper considered leukoemia of pyaemic nature, - started our Toxic Theory; and that in Virchow's writings, followed by those of Neuman, Ehrlich, Poppenheim, etc., we find our anatomical and cellular considerations of the disease, and the application, to its study, of the Cytogenic Doctrine. The Toxic Theory has remained a basis without any visible superstructure; the Cytogenic Doctrine has only revealed more fundamental facts, and given us theoretical and controversial interpretations of histological details without even attempting to elucidate the exciting causes responsible for these structural changes.

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Neither of these methods of inquiry deserve condemnation. Their failure may reasonably be attributed not to their guidance, but to the fact that this guidance has been allowed to remain uninfluenced by the most important fundamental facts; namely, etiological, clinical, and nosological facts, which undoubtedly constitute the most efficient pilots to a perfect conception of pathologic processes. We find from this literature that, to ignore these facts, apparently because of their obscurity, difficulty, and scarcity, has been the characteristic of recent research, which has limited itself to cytogenic investigations of the abnormal cellular elements found in these diseases. The Cytogenic Doctrine directs us to consequent phenomena and leads us indirectly to the study of their antecedents through such a hopeless theoretical maze and at present uncertain path, that we still find ourselves as ignorant of the path as we are of these antecedents. It is etiological and clinical study alone that brings us directly in touch with the antecedent phenomena of diseases. It seems, therefore, that both the inductive and deductive methods of inquiry should be employed to solve this problem and should hold a reciprocal relation to each other. If clinical observation is divorced from experimental pathology, progress is at an end. From a clinical aspect these diseases seem to be infective in origin;

it is chiefly the clinician who is impressed with the probable truth of the Toxic Theory, and the pure pathologist who is content to explain the condition as being a 'neoplasm,' or allied to tumor formation. The supporters of the Toxic Theory are practically the only observers who record, or attempt to record, aetiological and clinical details, and consequently find their task so difficult in the study of an obscure and comparatively rare disease, that they are unable to have a complete enough chain to follow, or to help others to follow, any definite line of inquiry.

(1)
 Froenkel was one of the first observers to formulate the idea of an oral and pharyngeal infective origin. He had the unique experience of observing ten cases of acute leukaemia in the course of a few months; and stated that, the constant and early involvement of the cervical glands in his cases was indicative of the disease possibly arising as the result of a pharyngeal infection. Trevithick's and Sternberg's (2) cases of chloroma, both gave a history of acute pharyngitis some weeks before the patients suffered from any symptoms or shewed any signs of the disease. Forbes and Longmead, (3) and Buchanan (4) are in accord with Froenkel's views and conclude "that the disease is so often preceded and accompanied by lesions of the alimentary canal from above downwards, permitting the entrance of some infective virus, that the possibility of an

infective origin is indicated." Martin and Mathewson⁽⁵⁾ also insist in the possibility of an infection from lesions of the alimentary tract. Their first case followed the occurrence of repeated attacks of swollen lips with subsequent glandular swellings in the neck, which the patient himself attributed to the state of the lips.

Seatcliffe, Hobhouse and Bushnell⁽⁶⁾, report a case of acute leukoemia giving a very suggestive history of infection following a scalded foot. This had not healed and apparently had caused an enlargement of the inguinal glands on the injured side. The glandular enlargement presented several haemorrhages or bruises, and had only been noticed by the patient three days before he sought advice. The general appearance so suggested a septic infection that the blood was examined for organisms. It was only found from a fuller examination of the blood, conducted a few days later, that the condition was one of acute leukoemia. Doctor Hobhouse further remarks, "As to the ultimate nature of the disease, whether it is due to an infection, or whether it is really a lympho-sarcomatosis of the blood, we are at present in the dark, the evidence is fairly equally divided."

Forbes and Longmead⁽⁷⁾ remark, that no growth however malignant, has ever been shewn to run so rapidly fatal a course of apparently not more than one or two weeks

duration, and that "the clinical picture shews strong resemblance to an acute infection, by the extremely rapid course of the disease in some of our cases, by the invariably raised temperature, and by the frequency with which a septic condition of the mouth appeared to mark the onset of the disease."

(8)
Abrastzow records two cases of acute leukaemia and considers one case to have undoubtedly contracted the disease from the other. The first was that of a hospital patient who had a sudden severe attack of epistaxis, requiring tamponing; shortly after this he became ill and feverish and developed an extensive purpuric rash, had entorrhagia and died. A blood examination during life, and the autopsy, revealed the nature of the illness. A month later the attendant who had nursed the case, was taken ill with purpura, epistaxis, and entorrhagia, and died fourteen days after the onset of symptoms, the blood shewing a typical leukaemic condition. The writer considered the first case as probably originating in an infection through an ulcer which was found on the soft palate post mortem. He is the only author who records anything resembling an infection. The comparative rarity of the disease, and specially the type of the disease, is certainly in favour of these facts being more than a mere coincidence.

Pollman and Penzoldt's⁽⁹⁾ case of acute leukoemia occurred in a child fourteen days after birth, when the red cells number 2.500.000 p.cm. and the leucocyte ratio was 1 to 8 - (an exact count was not stated); the condition was fatal four days later; and the post mortem shewed extensive vegetative endocarditis. Cultivations from the various organs were sterile. This case from its anatomical findings shewed a probable infective origin and certainly infective lesions; the authors regarded the condition as having developed in intra-uterine life, - although the mother was healthy, - and further state that no source of infection could be found, - the umbilicus was noticed to be apparently healthy.

It seems therefore that these rare cases of acute leukoemia have certain aetiological and clinical features accentuated which strongly suggest their infective nature, an opinion which I have further strengthened by personal experience.

The majority of chronic, and even some acute, cases develop insidiously and seemingly without any suggestion of infectivity; this is no proof against the toxic theory - parasitic or otherwise, since in the acutest form of osteo-myelitis, it is often impossible to determine the origin of infection; and since in tuberculosis we have the fact, that only recent lengthy experimental evidence, with an organism,

the life history of which we are well acquainted with, has given us some idea of the means and channel of its infection. Many cases of malignant endocraditis are equally baffling in this respect.

Traumatism has the same significance in leukoemic diseases as in infective diseases and neoplasms.

Leukemia has been known to follow an injury to such an organ as the spleen. I have myself noted chloroma following a simple dislocation of the elbow.⁽¹⁰⁾

V. Lembeck's statistics shew a considerable difference in the geographical distribution of the disease and its greater frequency in towns as compared to country districts; this, however, may be accidental.

Arnsperger⁽¹¹⁾ collected eleven cases of leukemia from the same region of the Euz Valley and considers this as pointing to an infective and endemic character.

Treadgold⁽¹²⁾ discussing the improbability of the infective theory cites Sanger's case - as evidence of his contentions - of a healthy mother giving birth to a leukoemic child; and Cameron's cases of a leukoemic patient giving birth to healthy children, some of which died subsequently of the disease. Pollman and Penzoldt's case, which I have quoted above, can according to his views serve as evidence against the infective theory. I do not consider this theory as being affected by the facts quoted, since Baumès-

Colles' law dictates the same phenomenon in syphilis an undoubtedly infective and microbic disease.

It is an undoubted fact that all acute cases and some chronic ones exhibit considerable pyrexia, in some cases accompanied by rigors and the appearance of petechial haemorrhages. It has been shewn that such symptoms have been considered by various authors - chiefly those who have had the experience of clinically observing cases of the acuter types - to be probably bacterial in origin, or at least suggestive of an infective process as causing the disease. Scott⁽¹³⁾ attributes this pyrexia to other causes:- "The fever occasionally met with in myeloid leukaemia and so frequently in acute leukaemia may be due to the presence of albumosis and peptones in the blood plasma, for it has been shewn that proteolytic ferments are liberated by the destruction of neutrophilic cells and large lymphocytes in the blood. These ferments are present in easily recognisable amounts in the blood plasma in myeloid leukaemia. Yet, on account of the clinical picture, acute leukaemia is frequently spoken of as if it were an acute infection. That secondary infection takes place is not to be wondered at, since there is little or no formation of defensive leucocytes. What is to be wondered at is that sufferers from a large celled lymphocytic leukaemia keep free from infection as long as they do."

There is no doubt that in myeloid leukoemia, - cases which occasionally shew a moderate rise of temperature, these products of proteolysis are invariably present in sufficient quantities to be detectable even in fresh blood (Erben⁽¹⁴⁾). Schum⁽¹⁵⁾ detected several varieties of proteosis in fresh myeloid blood; together with deuterio-albumosis peptone, as well as a casein digesting enzyme acting in an alkaline medium. Von Jaksch⁽¹⁶⁾ and others have confirmed these findings. But Erben⁽¹⁷⁾ moreover has shewn that fresh lymphatic leukoemic blood is both free from non-coagulable proteid, and if aseptically incubated at body temperature, proteolysis does not occur readily, and its products are only detectable after such time as to make it quite unreasonable to attribute the cells, found in cases of lymphatic leukoemia, with greater tendency to autolysis or proteolysis than any other normal cell. He further concludes that cells with neutrophilic granules, such as myelocytes, and polymorpho-neuclear neutrophiles, are the chief source of proteolytic ferments, and that these ferments originate in these granules, as such cells lose their granules early in the process of autolysis. For the opposite reasons he believes that eosinophile cells are much less active in this respect, and mentions the probability that coarsely granular basophilic cells - Mast cells

and basophilic myelocytes, - are also less actively proteolytic; in the first case because eosinophile cells resist proteolysis, and in the second because in cases of myeloma, with an increase in basophilic cells, he failed to find the normal proteolytic changes in the blood. Stern and Eppenstein⁽¹⁸⁾ confirm this absence of proteolytic power and also of non-coagulable proteids in lymphanoid blood as compared with myeloid blood. Since, as Scott himself states, this pyrexia is occasionally met with in the later cases and so frequently in the acute varieties of the former we cannot reasonably assume that such pyrexia is merely due to autolytic changes within the body; for, provided we can distinguish these two groups - myeloid and lymphanoid leukoemias, as always comprising two distinct groups, we see that in lymphanoid cases with a large celled leukoemia, we are almost invariably struck by the acuteness of the clinical picture, and it is in this group of cases that we have actually proof of the absence of any cellular ferments and autolytic changes, while in the myeloid group alone, - in virtue of the large number of granular elements in the blood, the blood is specially rich in these ferments, which are liberated - either through weakness of the cells, through the agency of ~~some unknown toxin, or through the fulfilment~~ of some unknown

toxine, or through the fulfilment of some unknown function by these cells. It is in these cases that the "acute" symptoms are moderate in severity.

On the other hand if we accept the view expressed in his paper that the change in type of cells of a given case of leukoemia is due to an expression of this cell developed becoming more or less hurriedly performed, and therefore that the disease really consists of two separable forms: one form affecting the undifferentiated cells of myeloid tissue (Myelogonien) and being actually myeloemias in their more chronic state, but also potentially lymphoemias (large celled) if proliferation overtakes development, when myeloblasts - the mother cells - predominate in the count; the second form including every small celled leukoemia, which starts in lymphanoid tissue, and which in similar circumstances becomes a large celled leukoemia because the circulating mother cells would be of the "lymphogonien type;" since the large lymphocytes ~~of~~ ^{is} an acute leukoemia ~~are~~ not identical with the large lymphocyte of ordinary type such as is found in infective diseases, in fact not a true macrophage*, but an

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Scott believes that the leukoemic leucocyte is a true large lymphocyte of normal blood for he says, "The ~~large lymphocytes~~ met with in the blood in acute leukaemia are not different from those met with at other times." This is a point which can be emphatically denied even on his own statement, "on all occasions a considerable number of the large lymphocytes were below the usual size (sic) and could only be distinguished from rather large ordinary lymphocytes by the fainter staining of their nuclei." The

undifferentiated cell, and in reality a progenitor of the lymphocyte (small) when derived from adenoid tissue, in which case such an undifferentiated cell corresponds to a "lymphogonien" of Benda; or a progenitor of the myelocyte when the cells arise from medullary tissue, and then corresponds to the "Myelogonien" type of Benda, or 'Myeloblasts' of Noegli, even then we see that the view that pyrexia is due to proteolytic ferments etc., is wrong from its most fundamental aspects. Firstly because, although it is a fact that proteolytic ferments are liberated by the destruction of true macrophages, we are lead to infer that these cells are not true macrophages, but 'mother cells,' and that there is no reason why they should form proteolytic ferments, neither is there any proof of this being the case. Secondly, we cannot maintain that such cells, found in acute cases of myelogenous origin, have the same autolytic capability during their myeloblastic phase, that they have in their more mature form as myelocytes; nor that those of an acute case originating in lymphoid tissue have acquired this property, because they have failed to develop into small lymphocytes - cells which are un-

leukoemic leukocyte is not a constituent of normal blood (see p.42) even Ehrlich's description, which is the source of this confusion in the minds of many hoematologists is that this cell is a large lymphocyte with the staining characteristics of a small lymphocyte.

doubtedly resist autolysis so effectively, that they can be recognised after six weeks incubation, outlasting all other varieties of cells. (K. Boden - 19).

The fact that Stykal, and Erben⁽²⁰⁾ found no uric acid increase in the urine of lymphanoid cases, but found this excretion of uric acid markedly increased in myeloid cases, and that Magnus Levy⁽²¹⁾ recorded an increased uric acid excretion in an acute case of ~~lymphanoid~~ leukoemia, only gives us an apparent support to the possibility that, since Erben's experimnts were apparently dealing with chronic and subacute cases, the leucoc¹ytic changes in acute cases ^{might be} ~~are~~ essentially different and dependent on these changes becoming more developed as a direct result of the cells being now of the large lymphocyte type, - whether true large lymphocytes or otherwise is immaterial. For it seems, according to Magnus Levy, - that this output of uric acid is inconstant, and that it has no relation to leucocytic destruction. This view of Magnus Levy's is disputed. However, further fundamental facts are available:- it is well established that many cases of chronic lymphanoid leukoemia have occurred shewing a large celled lymphocytosis, and conversely cases of the acute type are recorded with no large lymphocytes but with a small celled lymphocytosis alone, and even cases in which such a small celled leukoemia was accompanied by acute symptoms

fever etc., and in which no intercurrent infection could be found in spite of the most diligent search (Forbes and Longmead - loc. cit.).

It can, therefore, be safely asserted that if leucocytolysis is dependent on the type of cell present in the blood, it must also occur independently of the pyrexia, and cannot be considered its cause. On the other hand, if leucocytolysis is concurrent with pyrexia it cannot possibly have any relation to the type of cell present in the blood. As the hypothesis under discussion, that the fever may be due to the liberation of proteolytic enzymes, seems based on the fact that these enzymes are produced by two types of cells, neutrophilic cells, in infective diseases and in leukoemia, and large lymphocytes (macrophages) in infective diseases, it must be admitted to be untenable and quite inconsistent with our knowledge of the cellular, chemical, and clinical changes in leukoemia. It also follows from this, that proteolysis if it occurs specially in acute cases is most likely not the result of any autogenic factor.

It seems equally certain that if fever depends on the degree of proteolysis, neither the degree of proteolysis or the fever are caused by the number of leucocytes, for it is well known that acute cases shew a lower leucocyte count than chronic cases. Cabot⁽²²⁾

records a case which had 1'480.000 white corpuscles to the cubic millimetre, and lived for over six months after, when the patient enjoyed good health.

Treadgold⁽²⁾ discussing my statement that the clinical aspect of these acute cases suggested an infective origin, also mentions that the pyrexia may be due to the absence of the normal anti-enzymes in the blood serum, allowing autolysis, forming decomposition products and thereby upsetting the thermogenetic apparatus. Since we do not know that the same thing does not happen in acute infections, we must regard this as only a repetition of the almost unanswerable question as to whether the fever in infective diseases is directly due to bacterial toxins, or to the proteolytic changes induced by these toxins. We know that certain proteid poisons and "endotoxines" are liberated by heterolytic changes within the body, and are then capable of causing pyrexia; we also know that the subcutaneous injection of tissue extracts and enzymes are capable of causing toxic symptoms, (even like those found in leukoemic cases) - pyrexia, multiple hæmorrhages, fatty degeneration etc.,^(24,25,26) and that aseptic suppuration is also capable of considerably raising the body temperature. It is from such evidence that we have the possibility of fever in infective diseases being due not to bacterial soluble toxins but to the secondary proteolytic

changes produced. We must remember that the toxicity^{ci} of enzymes is a variable quantity, - papain is known to be highly toxic, while rennin to be slightly so, and its action to be soon destroyed by a very moderate rise in temperature; it is also to be remembered that the experiments of Hildebrandt, Achalmé and others do not justify us in accepting the hypothesis that autogenic enzymes have the same action; since they experimented with substances which were not cellular enzymes such as occur normally in the leucocytes or tissues, other than those specialised for the secretion of enzymes which are never present in the blood, but with such foreign and therefore toxic enzymes as trypsin, rennin, etc. When we come to study other varieties of enzymes we see the improbability of these enzymes being capable of any pyrogenetic action. Wells found that the injection of liver extract and blood serum rich in lipase gave almost no constitutional reaction. Observations during the resorption stage of a pneumonia offer the best material for this study, in as much as here we will not fall into the same experimental errors which are liable to occur when injecting organ extracts of one animal into another, or where we might be dealing with the formation of iso-anti-bodies. (See p.19).

(28)
Rzentkowski found the serum of pneumonia patients contained an increase of non-coagulable proteids - (it

may be mentioned here that the same occurs in leukoemia and has been considered as the cause of pyrexia) - this is due to proteolysis and absorption of the pulmonary exudate⁽²⁹⁾ a process which is usually more active, if not just beginning after the crisis. It would not be correct to attribute the absence of temperature in some cases of delayed resolution to the possibility of a precritical immunisation against these proteolytic ferments and their products. We have here then no fever resulting from an exceedingly active proteolytic process involving the absorption of a large exudate - possibly because both the exudate and these ferments are in a sense 'autogenic' in origin. Clinically we have only an apparent contradiction in cases of moderate internal haemorrhages (haemo-peritoneum haemo-thorax, or Haematoma) which are accompanied by fever - attributed to the action of the fibrin ferment. If we carefully analyse our facts and theorise from clinical and biological aspects, we find that this is only an apparent paradox - even if we accept the logical assumption that this fibrin ferment can act as a pyrogenic agent.

Rolly⁽³⁰⁾ points out that fever in infective diseases is not harmful to the organism and further concludes from his experiments that the observations of Leibermester on the harmful effects of fever and its production of parenchymatous degenerations are

incorrect. Unverricht Adami and others are quite in accord with Rolly's opinion, that such fever is purely a reaction on the part of the body to promote phagocytosis, overcome bacterial invasion, and form the necessary anti-bodies more rapidly, and that the occurrence of a hyperpyrexia is due to an 'over-compensation,' which Weigert has shewn is a common property of living matter and which manifests itself more commonly in pathological conditions. Rolly and Meltzer further shew that human leucocytes were more active at a temperature ranging between 39.5 and 40° Cent. This seems undoubtedly to shew that phagocytosis etc., is not the cause of fever but rather that the fever is in some ways produced to help phagocytosis to become more efficient. In the formation of fibrin we may have therefore a means of elevating the temperature to answer every purpose in the economy of the organism. In internal haemorrhage the process of clot formation not only acts as a means of easier absorption of the haemorrhage but also seems to raise the temperature sufficiently to help absorption by promoting phagocytosis. It is the experience of most surgeons that fibrin pyrexia is not of longer duration than a few hours and that actual absorption of the clot is not accompanied by any fever. In infective diseases it is not difficult to see that the same changes may initiate the process of defence. In

pneumonia we have usually an elevation of temperature as long as the fibrinous exudate continues to form as is indicated by the post-critical reappearance of chlorides in the urine, and what is of greater theoretical importance is the fact that the temperature remains normal during proteolysis and absorption of fibrin products into the blood - as evidenced by the post-critical metabolism, the increase of non-coagulable proteids in the serum and the occasional persistent leucocytosis. It is even doubtful if such a substance as fibrin is capable of elevating the temperature. E. Zurhelle (Wien. Med. Klin. Nov. 7th, 1909) states that clinically this pyrexia in clot formation is manifested a considerable time after the appearance of the clot and attributes this and the findings of Lusbarsch to a secondary infection. He also found that fibrin was by no means a constant constituent of a clot. It seems most unlikely therefore that such proteolytic ferments, and their products, are capable of causing pyrexia, and certainly there is no experimental proof that they are capable of producing antibodies. If we consider such 'lytic' substances to consist of the combined actions of amboceptor and complement, we have the establishment of the above in Ehrlich's experiments. He has shewn that the injection of red blood cells of a particular animal into another of the same species, demands the

formation of an immune body which is active only towards the red cells of other individuals of the same species, and of the animal from which the red cells were derived. In other words such an immune body is an 'iso-lysin.' He was quite unable to demonstrate experimentally the theoretical possibility of the formation of an 'auto-lysin,' - a lysin active towards the red blood cells of the same individual injected; - and even of such an auto-lysin being held in check by an 'anti-auto-lysin.' He further explains that a 'Horror Intoxicus' is avoided by assuming that the receptors of the body cells of the immunised animal have no corresponding haptophore group to anchor the haptophore group of the lysin, which is thus inactive and therefore only on iso-lysin. If we accept this we see that the same animal for the same reason is also incapable of forming an anti-autolysin, i.e. because the receptors concerned do not fit.

(31)

Ehrlich and Morgenroth close their paper describing these experiments by saying "...we should like to point out that the difference between iso-lysins and autolysins emphasised by us makes several recent attempts directed to the solution of certain pathological processes, particularly those of autointoxication in man appear questionable. It has frequently been ascertained that serum secretions and excretions of the diseased body are poisonous in animal experiments

and the conclusion has been drawn that the substances to which this poisonous action is due must exert an injurious effect on the organism of the patient. From the above analysis we see that this conclusion is not at all imperative. If for example, the serum of a scarlet fever patient is especially toxic to guinea-pigs, it is possible that the same may be absolutely harmless to the patient himself. Even if one demonstrates that the serum of anæmic individuals dissolves the blood-cells of other individuals, it does not prove that this property is of any significance in the origin of anaemia. On the contrary, it is highly probable that this hoemolysin is only an isolysin and not an autolysin."

This incapability on the part of the tissues to form antibodies against themselves, is also the salvation of an individual that has sustained an injury causing an internal haemorrhage, or a haematoma. If this were not so antibodies would be formed which would cause serious and fatal hæmolysis! The same protective changes possibly occur in the resorption of an infarct.

According to these two authors⁽³²⁾ this protective mechanism is extended to the complement. Ehrlich shews that the serum of a rabbit which had been immunised with blood-cells and serum of an ox, contained

an anti-complement, which was present in this rabbit's serum in sufficient quantities to inhibit the action of a specific haemolysin completely. Since he cannot conceive what use it would be to an individual in its economy, for the idio-complements to form anti-complements, and since he failed, time after time, to obtain an anti-complement by injecting sheep with goats' complement, and vice versa - he concludes that such complements being identical - even in allied species - they cannot excite the formation of antibodies. In the case of rabbits injected with ox, or goat complement, he ascribes the formation of an anti-complement to the assumption that the injected complement of the one animal possesses the same haptophore group as the complement of the other (because the anti-body of one is capable of neutralising the complement of the other), but that they differ in the zymophore group, and that this difference in molecular construction is sufficient to act as a "foreign complex" capable of being anchored to the "complementophile group" of the cell (also because two haptophore groups are similar in both cases), which in response to this foreign exerting stimulus thrusts off the corresponding side-chains (amboceptors), ~~which~~ ^{as} ~~are~~ formed anti-complements, in sufficient quantities to neutralise and inhibit the idio-complements, this

renders any other anti-body (such as a haemolysin) incapable of haemolysis through need of a complement.

It seems to me therefore, that if idio-complements or any other autogenic body, whether complement or amboceptor does unite with the cell, in virtue of the cell possessing fitting haptophore groups, the resulting 'complex' not being a foreign one, and therefore unable to exert any damaging stimulus, would be assimilated and utilised by the cell for its own economy by causing it to thrust out a similar and almost unaltered body, - i.e. by this complex acting as a food in the broadest meaning of the term; the cell thus attaining the result of keeping, if not perfecting its means of defence, with the minimum expenditure of energy. If the alternative happens, it is easily seen that the result will mean a greater expenditure of energy in the thrusting out of innumerable anti-bodies to the ultimate destruction of the organism a state of things which is not only a paradox but absolutely incompatible with biological laws.

We have certain facts in the study of natural immunity which seem to contradict this. Metchinakoff⁽³³⁾ states that a scorpion is not only immune to its own poison, but that its blood has marked anti-toxic action on the venom, since a lethal dose when mixed with scorpion blood was incapable of producing intoxication when injected into a mouse. There is however,

no reason at all why these antitoxic properties should be considered to be due to an anti-toxin in the sense of a formed specific anti-body (amboceptor) having the special function of inhibiting this special poison. If we study the matter more closely, we find that we are dealing with a most intricate and difficult subject, but one which fortunately does not affect any contradiction of the above, either on facts, or on the explanation of these facts, unless we adopt an explanation which is fundamentally wrong. Metchnikoff (loc. cit. p.384) has also observed the same antitoxic power of cray-fishes' blood injected into mice, - though cray fishes quickly succumb themselves to the action of the venom, and the blood of one cray fish will not protect another from scorpion venom. It is more than absurd to imagine such phenomena to be dependent on the occurrence of an immune body, and even more absurd to speculate as to the probable origin of such a hypothetical body! To avoid any possible misunderstanding it is best to consider the matter fully. Metchnikoff (p.389) explains this apparent paradox by assuming the absence of either the requisite 'cytase' (complement) ^{or the} of 'fixative' (amboceptor) elements for the neutralisation of a toxin, and in doing so accepts Kretz's hypothesis that an antitoxin has the same double mechanism - cytase and fixative - as anti-microbial substances.

Although Ehrlich, Wasserman etc. do not agree with Kretz and Metchnikoff, it will be seen that this difference of opinion will not affect the case under consideration, for scorpion venom is a zootoxin, consisting exclusively of amboceptors (fixatives) and having the same mechanism as an anti-microbial substance, or a haemolysin procured from an immunised animal. It is only when we come to consider antitoxins that the two theories imply a difference in mechanism. Ehrlich's teaching is that antitoxins act as single bodies without necessitating a complement, and that anti-haemolysis are also single bodies directed chiefly against the complement or the amboceptor.

It has been shewn by Kyes⁽³¹⁾ that cobra venom is a cellular poison only when activated by serum complements or by "endo-complements" (lecithin). We have every reason for believing that scorpion venom has a similar mechanism, hence it must follow that cray-fishes' blood contain the necessary complements (cytases) to so activate the venom as to render intoxication possible. It is unlikely that the toxic action of the venom is complemented "in vivo" by these "endo-complements" only, for then this toxic action would be slight and transitory and would be inhibited by cholesterol etc. (Kyes l. c.). It seems inconceivable that a true antitoxin or a true anti-body -

whether it is independent, as Wasserman states, or not as Metchinakoff holds, on a complement, could remain inactive in such a serum. We must therefore attribute these phenomena not to a rupture of the amboceptors of the venom by an anti-amboceptor, but to a rupture of the complements by certain anti-complements present in cray-fishes' blood. If we take this conclusion we will readily see that these anti-complements are inactive against the complements originating in the same blood; in other words they are iso-anti-complements, for they allow the complement to exert its power of activating the venom amboceptors when the venom is injected into a cray-fish, such an inactivity on the part of the anti-complements being only what is to be expected when we realise the improbability of autogenic anti-bodies being capable of neutralising autogenic complements or amboceptors.

When however cray-fishes' blood is injected into a mouse, the anti-complements of the cray-fish inhibits the complementary action of the mouse's serum, while the complements contained in the cray-fishes' blood are either insufficient in number or not specific enough to activate the venom themselves.

This attitude is not difficult to adopt when we know that Morgenroth and Sachs⁽⁵⁾ experimenting on the quantitative relations between amboceptor, complement

and anti-complement, shew clearly that the required amount of anti-complement to inhibit any complementary action does not depend on the amount of complement but absolutely on the amount of amboceptor - in this case the venom.

We have two more things to consider. Firstly the fact that complements are less 'specific' than amboceptors; on this depends the Wasserman Bordet serum reaction, etc. There is therefore no reason why the anti-complements in cray-fishes' blood should not inhibit mouse complement. Conversely, Ehrlich has repeatedly failed to obtain an iso-anti-complement even by the injection of serum (containing complement) of one animal into the body of an individual of an allied species⁽³²⁾; "Thus, neither sheep when injected with goat serum, nor, conversely, goats when injected with sheep's serum produced any anti-complement, for these species manifest an extensive similarity in their complements." This also shews that this 'specificity' is also marked in the opposite direction, i.e. that although they behave 'in corpore' in the same way as they behave 'in vitro,' being used practically in the same way as the idio-complements of an individual of an allied species, yet their injection into an individual of an allied species will not produce an anti-complement. Such actions on the part of complements readily explains the fact that

Metchinakoff quotes:- that the injection of cray-fishes' blood into another cray-fish will not have any protective action, because such an anti-complement would be too similar in construction to the anti-complements of the second cray-fish to have any effect in neutralising the idio-complements.

There is no reason against assuming that scorpions' blood itself also contains similar anti-complements, and that its antitoxic powers also depend on these bodies. The immunity to its own poison may depend upon an unsusceptibility - inexplicable as yet - on the part of its own cells.

That "Complement Blocking" occurs experimentally can neither be denied, nor be said to disprove this.

Secondly, Ehrlich, Marshall and Morgenroth⁽³⁶⁾ criticise Besredka's ("Les anti-hoemolysins naturelles"- Ann de l'Inst. Pasteur, October 1901) by demonstrating and insisting on the plurality in type of amboceptors (anti-hoemolysins) in normal sera and by shewing that in neutralising one type of amboceptor derived from normal horse serum, other hoemolysins are left which are specific for cells of a different species. It is absolutely illogical to believe that such a plurality in anti-amboceptors can arise autogenically as the result of self immunisation. These authors state that:- "There is no doubt at all that

anti-amboceptors exist in normal serum; this was first proven some time ago by Ehrlich and Morgenroth and also by P. Müller. These anti-amboceptors do not, however, occur regularly as was also pointed out at the time.

Our analysis therefore shows that since the ' fundamental fact does not apply, the extensive theoretical conclusion drawn by Besredka from the exclusive protection of the homologous blood-cells by the serum cannot be recognised. That the amboceptors present do actually primarily protect the blood-cells of the corresponding species is probable in itself, for according to our views as mentioned elsewhere, they represent free cell receptors. Besredka assumes that the reason for the development of his suppose anti-amboceptors is this: that blood-cells, which are constantly dying in the organisms, cause the production of hæmolysins. These would endanger life if the organisms did not paralyse their action through the development of anti-amboceptors. Such a regulating contrivance can surely not be very common, since it was not observed by Ehrlich and Morgenroth in their numerous experiments on isolysins, in which it would most readily be discovered. But if such contrivance were a necessity, it would have to be constant. This however, is not at all the case as we have already established.

The simplest and most natural assumption is that the anti-amboceptors are nothing else than products of cell disintegration, free receptors which are capable of binding amboceptors and so exert a deflecting influence. The assumption that these free receptors are products of retrogressive metabolism is borne out by the fact established by Schaltenfroh that they are excreted through the urine in considerable amounts."

We therefore see that we can take it as an established fact that at least a certain class of proteolytic substances - autogenic substances - are neither toxic nor capable of exerting any harmful action, either in destroying the cell or in the formation of anti-bodies.

We come now to the most theoretical of all considerations, namely the so called enzymes and anti-enzymes formed in the body tissues and exudates. Theoretical because we know practically nothing of their nature. We know however that the fundamental principles of their action are of a catalytic character, a reversibility of chemical action, chemical synthesis, and an attempt to the establishment of an equilibrium. ^{**} The work of Korschum ⁽³⁷⁾, Walker ⁽³⁸⁾ and

** If metabolism is governed by bodies having such fundamental properties, it is difficult to see the necessity of inhibiting "anti-enzymes."

others makes us agree with Oppenheimer, that the relations between enzymes and toxins appear closer the more we study the subject. Some "enzymes" at least have been shewn to possess a specific amboceptor and a non-specific complement (kinase) and behave as if their action was dependent on haptophore and toxophore groups. All the evidence seems to shew that the "normal anti-enzymes" are non-specific. Von Eisler⁽³⁹⁾ found that human serum is less resistant to human trypsin than pig-serum. Jacoby⁽⁴⁰⁾ has also shewn that autolytic enzymes derived from organs are more active and specific for the cells of those organs. It is on such evidence difficult to recognise the presence of a specific anti-enzymes in these organs. Cathcart⁽⁴¹⁾ found anti-trypsin in a variety of sera and considers it non-specific. I do not see any reason why we should not adopt Oppenheimer and Arons' view⁽⁴²⁾ regarding the nature of these normal anti-enzymes and consider this resistance to depend upon the configuration of the proteid molecules of the serum containing the anti-enzymes, these when in an uninjured condition presenting no suitable surfaces for the attack of the ferment. This view has practically the same application in the case of the normal anti-enzymes as Marshall and Morgenroth's definition of the nature of normal anti-haemolysins.

Personally I would not be surprised to find in myeloid blood a diminution of anti-ferments for it can almost be taken as a working rule that proteolytic anti-enzymes vary in pathological fluids conversely with its albuminoid content and inversely with the numbers of neutrophilic cells. A fact which in itself tempts one to believe from what we know of immunity, that in this variation we may recognise a means of defence.

⁽⁴³⁾
 Moragliano has found that these anti-ferments are frequently absent or diminished in inflammatory exudates etc. We know that many bacteria themselves contain proteolytic enzymes which are in themselves capable of neutralising or inhibiting any anti-ferments, we must therefore admit that even if this diminution of the normal antienzymes in the serum were the cause of proteolysis etc. in leukoemia or of the leukoemia itself that the infective or toxic theory still remains uninfluenced. Even if we allow that such a condition as a loss of these anti-enzymes occurs from whatever cause in leukoemic blood we can not agree that pyrexia in certain cases is due to these proteolytic enzymes being able to exercise their action; for cases undergoing X-ray treatment shew by the blood picture, urine metabolism, etc., that these leucolytic changes are markedly increased, not with an elevation but with an abatement of the temperature

in some cases, and in a great majority with very marked benefit.

As to the occurrence of intercurrent infection we must repeat the fact quoted above. That in acute leukaemia intercurrent infections are less liable to take place than one would expect, is true enough in one sense, but if we examine our facts more deeply, we find that such a resistance to infection in acute leukaemias is natural as well and true enough. It is sufficient to see the very few cases in which an intercurrent infection has been proved to have been the cause of death, and the few cases in which the occurrence of such a general infection has been known to occur. Even post mortem cultural examination often fails to reveal the presence of organisms in the tissues and blood. Froenkel obtained negative results in two cases examined specially. Forbes and Longmead obtained cultures of streptococci in five out of seven cases. Out of four cases I have only obtained a growth - which I regarded as a contamination - in one case, from the liver. In every case a culture was taken from the heart's blood, spleen, liver and glands and bone marrow. Further in leukaemia resistance to infection is not so very much impaired, as any suppuration present is attended with pus formation consisting exclusively of polymorphs and lymphocytes.

Bearing all these points in mind we may safely consider that increased proteolysis is not directly responsible for the development of acute symptoms; that leucocytolysis does not depend on the type of cell, and that if it does depend on such a thing as a loss of anti-enzymic action the parasitic or toxic theory is far from being disproved.

Of great importance from the toxic aspect of the disease is the extremely common occurrence in acute cases of hoemorrhagic rashes. From a careful enquiry into the previous history of my cases, from their clinical course and from the literature of other acute cases, I believe certain facts in connection with these rashes need emphasising.

Cases then exhibiting a hoemorrhagic rash may be divided broadly into two groups.

(a) Those cases with a marked hoemorrhagic rash which seems to, or actually does, mark the onset of the disease. Such cases are usually associated with some septic condition, either before or at least concurrently with the appearance of the rash.

(b) Cases which may or may not belong to the first group, but which show throughout their clinical course a similar though less extensive rash lasting only for a few days and recurring irregularly at intervals, which seem marked by more pyrexia and an

aggravation of constitutional symptoms, but only followed by marked changes in the cellular elements of the blood.

That such haemorrhages should be considered as either a mechanical rash due to the blocking of capillaries by large lymphocytes etc. or to an altered condition of the blood plasma "resembling purpura" are obviously considerations that are unworthy of serious criticism. Such rashes are always toxic, and the toxine causing them does not seem to originate in the breaking down of leukocytes; for in such cases as "acute pseudo-leukoemia" where it would be difficult to conceive such a possibility, we have the same identical rash appearing (Erbstein⁽⁴⁴⁾). The fact that epistaxis, hoemothorax etc. may complicate the clinical picture is to be attributed to no other cause than the same unknown toxic mechanism affecting similarly the submucous and subserous surfaces, together with the diminished powers of coagulability which characterise the disease. It is quite compatible with fact that both septicaemias and leukoemias which have shewn no subcutaneous haemorrhages or rashes, and no clinical signs of sub-mucous or sub-serous haemorrhages, may shew and do shew on the post mortem table marked subserous petechiae.

II.

The leukoemia itself - the actual blood picture which is considered characteristic of the disease, may be said also to constitute the living basis on which we apply the Cytogenic doctrine to build up our knowledge of haemogenesis. This knowledge must obviously be so theoretical, and so unstable, that to avoid using severer criticism, we may call it undeveloped as an explanation of its changing and conflicting character. Even a comparison of the various teachings will only reveal a few points which do not seem to be contradicted, but which cannot for this reason be considered as proven. In general it can be said that in the study of this disease and to explain the presence of the leukoemia, we always arrive at the same conclusion and assume a hypothetical stimulus or 'noxa' as expressed in Poppenheim's theory.

To ignore the toxic theory purely because no known infective disease manifests the same cellular changes in every respect, seems both illogical and to be as dangerous a barrier to the progress of knowledge as it would have been some years ago to condemn the teaching ^{by assuming} that the malaria parasite was not a parasite on the grounds that no similar disease had been known in

man. There is no reason whatever why these 'noxoe' or 'stimuli' should not be directly or indirectly dependent on a parasitic origin.

If for the sake of the present argument, we put aside the cytogenic doctrine, we are left with certain ætiological and clinical facts which analysed together with those observed in infective diseases, indicate an infective origin in these conditions. These facts are in themselves so scanty and difficult to obtain, that they can easily be obscured, and have been even contradicted by such a mass of negative evidence, as to make us ignore certain lessons that the evolution of our knowledge of disease in general has or ought to have taught us.

It is surprising that this negative evidence, though in reality of the most theoretical quality, has been responsible for the crushing of the toxic theory. It is even more surprising when we know that all such negative evidence, especially when dealing with a rare disease of unknown pathogenesis, is essentially misleading. No better proof of this is conceivable than the notions at one time entertained regarding the origin of tuberculosis - chaos of hypothesis and empiricisms which were only purified by Koch's discovery, and which allowed teaching to be as erratic in its quality as the fashion! - Tuberculosis in a very short time became an inflammation, a neoplasm, a

molecular disintegration and even the usual kismet of a hereditary tendency. A state of affairs which truly meets a fitting equivalent in the present teaching of the origin of leukoemia; only now, thanks to Virchow's work on cellular pathology, our speculations have been forcibly restricted to narrower channels.

Since any fruitful pathological enquiry seems to be that which is dictated chiefly by ætiological and clinical study in the first place, and in the second, by cellular changes, we must in the first place adopt the toxic theory and secondly compare the cellular changes found in leukoemia with those of known infective diseases, and see if by this comparison we find sufficient analogy in the changes to render their interpretation more easy and to recognise the nosological position of leukoemia.

The importance of this lies in the fact that such a comparison seems the truest method to adopt, since it is only by comparing "effects," the "cause" of which we already know, with "effects," the "cause" of which we do not yet know, that we can enlarge our knowledge. For this reason it seems that the present tendency, of regarding leukoemic diseases as a benign or malignant hyperplasia deserves the severest condemnation; we know nothing about the causes of

new growth formation and although it seems a convenient method of answering this complex problem, yet its solution will obviously never be found in such an answer until we are familiar with the causes of new growth formation. The heading of 'neoplasms' at present only apparently disguises our ignorance of any obscure disease shewing pronounced hyperplasia or so called 'embryogenic retrogression.'

The views so repeatedly expressed that leukoemia is a benign neoplasm affecting the germ centres of leucocytes and that it is sometimes - Chloroma and acute leukoemia - so quickly fatal, not because of its malignancy, but because of the vital parts affected, stands in complete contradiction to the view equally forcibly expressed, that these conditions are true sarcomata. It will be shewn later that the occurrence of true metastasis in chloroma is rightly considered by many authors as doubtful, and that the cells constituting the lesions, and the characters of the lesion, differ fundamentally from those found in sarcomatous lesions. To consider certain cases of acute leukoemia as a sarcoma of these centres is not compatible with fact, for some of these cases shew no lesions which might even at first sight be mistaken for metastatic deposits of a sarcomatous nature.

Again, such rapid proliferation as occurs in either of the above class of cases cannot be reasonably

ascribed to a benign hyperplasia. I have observed one case of acute leukoemia which gave in little over one week a rise in the blood count from 10,000 white blood corpuscles per c.m.m. to over 200,000.

Variations in the size of the glandular and splenic enlargement, in the rate of progression of this enlargement, and in the number of leucocytes, are so frequently observed in leukoemia as a characteristic of the disease itself, that the so called analogy between leukoemia and benign growths has a doubtful existence.

Cases of true sarcoma undoubtedly do occur shewing a blood picture indistinguishable from leukoemia (Toje's case and others). These cases are however accompanied with a lymphocytosis, yet it is difficult to consider these lymphocytes as forming part of the sarcoma itself - a fluid sarcoma in a unrestricted sense, for we find that the sarcomatous change has not spread any more quickly or diffusely, than in cases with an ordinary leucocytosis, in spite of the fact that many of these cells are found both in blood and lymph channels, and in the interstices of connective tissues. This at once disposes of the idea that each of these leucocytes are capable of forming metastases. Again cases of sarcoma have occurred, shewing ordinary round or spindle cells in their lesions, with a high leucocytosis and such a relative

increase of myelocytes, as to lead to a possible error in diagnosis.

In comparing, later, the morbid anatomy and cellular changes of the two conditions, neoplasms and leukoemia, we will find further points of difference while will increase this separation; let us for the present consider the other side of the question:-

The quantitative changes in leukoemia are sometimes met with in infective diseases. Cases of abnormally high leucocytosis in infective diseases are quite as common as cases of hyperpyrexia; and both hyperpyrexia and hyperleucocytosis are particularly liable to occur in certain diseases. In whooping cough this hyperleucocytosis may be marked. In some cases of pneumonia and of empyaema the leucocyte count may be surprisingly high. Loher records a case of pneumonia which gave 114,000 per c.mm. and Cabot one with 100,000; Bunting⁽⁴⁵⁾ reports Saundby's case of empyaema with a leucocytosis which rose to 214,000 per c.mm., the differential count showing no abnormal forms. Bunting further adds, "Neither in my own experience nor in the literature on the subject of leucocytosis, have I found a leucocytosis even approaching that noted in the last observation, apart from spleno-medullary leucocythaemia." Muir's case of empyoema is one case which was overlooked by Bunting

It is possible that such hyperleucocytosis occurs oftener than we know of and escapes observation for the simple reason that a blood count is not undertaken as a routine practice.

Such hyperleucocytosis may have the same significance as hyperpyrexia and possibly be due to an 'over-compensation' on the part of the bone marrow.

Muir⁽⁴⁶⁾ discussing these quantitative changes mentions a case of empyoema in which the leucocytes amounted to 93% of all the cells in the blood, and further states that:- "On this point my results agree with those of Ehrlich and Einhorn. It is accordingly quite incorrect and unscientific to separate leucocythaemia from leucocytosis by the mere number of leucocytes....the difference....is one also of quality and not of quantity alone.... I believe that the changes found in leucocythaemia cannot be explained by any other theory than that of an indefinite proliferation of a certain kind of cell, in its nature resembling that seen in the growth of many tumours."

In certain infections myelocytes are found in the blood (malaria, tertiary and congenital syphilis, pneumonia, diphtheria etc.). Schnidler⁽⁴⁷⁾ regards a relative myelocytosis which remains after the fall in number of the other leucocytes, as occurring in fatal infections, and due to exhaustion, or inhibition of the bone marrow. Myelocytosis is known to occur in

tumour growth affecting the marrow tissues, and is then attributed to "mechanical irritation etc."

Since we are no more liable to find myelocytosis in osteo-myelitis, than we are in ordinary septic infections of the same gravity, which do not affect the bone marrow locally, it is highly probable that this view is incorrect.

Muir⁽⁴⁸⁾ found that injections of staphylococci into rabbits in large dosage caused the passage of myelocytes into the blood stream. Engel, Cabot, etc. consider the presence of these myelocytes in the blood as indicating a bad prognosis. It appears that on these grounds alone rests the idea that such a mixed leucocytosis is due to a negative chemiotactic action of the toxine, or to an exhaustion of the bone marrow. According to Muir it is often the case in suppuration that each c.cm. of pus contains about 1,000,000 polymorpho nuclear neucocytes. It is therefore obvious that where there is a copious daily discharge of pus, the production of white corpuscles is quite as enormous as in the most marked leukoemia, still no myelocytes may appear in the blood. Conversely in tertiary syphilis the leucocyte count may only shew a slight leucocytosis together with as many as 10% myelocytes. It seems unlikely therefore that the presence of these cells in infective diseases is due

to a negative chemiotaxis in any way. Neither are we justified in saying that the sole function of these cells is the generation of riper leucocytes, polymorpho nuclear cells etc.

Unfortunately any conclusion we can come to regarding this or any other possible function of myelocytes must necessarily be based on the most theoretical grounds, which at present only consist of a histological comparison between polymorpho nuclear leucocytes and myelocytes.

We find that these two types of cell exhibit similar granules in their protoplasm. Sherrington⁽⁴⁹⁾ has shewn that the eosinophile granules of polymorpho nuclear cells in the horse are cuboid, spherical in the rabbit and rod-shaped in dog's blood, and that the eosinophile granules of myelocytes in these animals are similar in shape. Ehrlich also considers the neutrophilic or 'E' granules found in human polymorpho nuclear cells and myelocytes as specific for man in size, shape, and staining reaction. Ehrlich, Buchner and others regard these granules as being the source of an intra-cellular secretion. This view seems highly probable, from what we know of the physiology of other granular cells, and from the fact that in myeloid blood, there is a marked richness in proteasis etc. The same function has been also theoretically considered in the case of eosinophile granules (Buchner⁽⁵⁰⁾)

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Kanthack and Hardy⁽⁵¹⁾, Laschtschenko⁽⁵²⁾ and Traumsdorff⁽⁵³⁾

Metachinakoff and Mesnil⁽⁵⁴⁾ however, do not accept this view; the former⁽⁵⁵⁾ compares these eosinophile granules with those formed by bacterial debris as the result of intracellular degestion. Referring to this eosinophile transformation he says, "It is probably widely diffused among phagocytised bacteria. This fact demonstrates clearly that at least some of the eosinophile granules are derived from foreign bodies ingested by phagocytes. Others are probably the result of the transformation of soluble substances absorbed by the phagocytes." He continues (l.c. p.190) "it is no longer possible to maintain the bactericidal secretion by leucocytes or by any other category of cells. The bactericidal substances do not circulate in the blood plasma nor in that of the exudate and this is a sufficient reason for refusing to it the title of a secretion product. Its presence in the blood serum is due, like that of the fibrin ferment, to the destruction, or more or less grave injury, of the phagocytes." There is no doubt much can be said in favour of these seemingly contradictory views of Metachinakoff's and Ehrlich's. These granules have been shewn by Weis⁽⁵⁶⁾, Posner⁽⁵⁷⁾, Kossel⁽⁵⁸⁾ and Barker⁽⁵⁹⁾ to be highly albuminous and to contain iron. It has already been said that Erben found these granules to differ from neutrophilic granules, in apparently not being the source of proteolytic enzymes.

Since eosinophilic myelocytes occur in the marrow, we cannot accept Metchinakoff's explanation of these granules too literally. The alternative therefore, is to regard these cells as being really 'over-fed' cells and that their granules represent the stored up albuminous and ferrogenous substances which may be concerned in the supply for building up of other leucocytes. That eosinophile leucocytes are also capable of phagocytosis is an undoubted fact, and one which leads to the theoretical conclusion of attributing this to the necessity of more quickly changing the molecular construction of the albuminous substances constituting the granules, to meet the requirements of immunity. The fact that these cells usually disappear altogether from the peripheral blood, and usually reappear just at the time when the body has got the upper hand of a particular infection, that they are rarely vacuolated, (Buckmaster l. c. p.74) and that they are less actively phagocytic, seems to indicate that their function is less that of phagocyte, and more that of a means of conveying certain substances from one part of the body to another, - possibly their altered granules to the manufacturing centres - so that these can produce a more potent generation of leucocytes.

While Metchinakoff and Ehrlich disagree on the secretory theory of bactericidal substances, it will

be seen that the contention of these two authors will admit the view that phagolysis and the shedding by neutrophile cells of certain substances contribute to the defence of the organism against infection.

Metchinakoff (l.c. p.551) allows; "When micro-organisms are introduced into those situations which contain pre-existing leucocytes, the leucocytes under the influence of the shock undergo serious lesions accompanied by the throwing out of cytases. Under these conditions the least persistent micro-organisms exhibit undeniable signs of deterioration....and may even die in greater or lesser numbers. When however, the leucocytes are well protected and withstand the infection of the micro-organisms without being profoundly altered, the extra cellular destruction of micro-organisms does not take place. On the contrary a very rapid phagocytosis produced which bring about the death and intracellular digestion of these micro-organisms. Under these conditions vibrios are also transformed into granules and perish but only within the leucocytes."

These facts are well demonstrated experimentally, & we may on their account consider the appearance of such non-phagocytic & easily disintegrated cells with neutrophilic granules in the blood of patients suffering from certain infective diseases, as due, not to a negative reaction on the part of the bone marrow, nor

to an accidental occurrence caused by irritation, etc. but to the probability that phagocytosis in itself has been an insufficient defence, and that myelocytes, because they have the property of ready disintegration, and of containing the same granules, perhaps in larger quantities than in polymorpho nuclear cells, are called forth as an additional mechanism or as an exaggeration of part of the usual mechanism of defence. This would also explain the fact that these myelocytes are more common and abundant in diseases in which the infection is specially severe, and in cases of more chronic infections where phagocytosis has not been so perfectly effective. It seems, then, that for all purposes of defence the polymorpho nuclear leucocytes show chiefly the capability of phagocytosis, and to a marked but less extent, of phagolysis, and that myelocytes are chiefly adapted to phagolysis, and less if at all to phagocytosis. This question should be settled experimentally possibly by determining the presence or absence of myelocytes in the blood and in the peritoneal cavity in animals which shew Pffeifer's phenomena etc.

In considering the other type of cell found in leukoemia, we find ourselves in no less difficulty. The lymphocyte found in leu κ oemia and chiefly in chloroma and acute leukoemia has been until recently

considered to be of the same type as the large lymphocyte found in acute infections. The idea that this type of cell is essentially different, and that it is exclusively found in leukoemia is fast gaining ground. The description - by the various authors - of this cell is by no means uniform, a fact which has lead to much confusion and delay in the formation of opinion.

Grawitz⁽⁶⁰⁾ called them "unrieffe formen" and considered them specially liable to fragmentation, and incapable of further development in the blood, and moreover separated them from the ordinary lymphocyte as constituting a separate class of cell. Ehrlich and Lazarus⁽⁶¹⁾ and Engel⁽⁶²⁾ described these cells as being large lymphocytes with the staining and other characteristics of small lymphocytes. The works of Ebstein⁽⁶³⁾ and Benda⁽⁶⁴⁾ have lead to the opinion that these cells consist of two kinds - one identical with the latter's "Lymphogonien" when originating in lymphatic tissue, the other, with his "Myelogonien" when from medullary tissue. The other view is that these cells are all undifferentiated marrow cells - "Myelogonien (Benda) "Myoblast" (Noegeli) "Lymphoid marrow cells." (Türk).

Buckmaster (l. c. p.82) considers the different reaction to staining reagents to be as follows:-
"With methylene blue the nucleus stains less intensely than that of other lymphocytes the protoplasm on

the other hand stains less deeply. This possesses an exceedingly fine compact granulation but with tri-acid no genuine neutrophile granules can be demonstrated....I incline to the opinion that many of the cells identified as large lymphocytes in leukoemia are never seen in normal blood and that no lymphocyte comparable to these exist. Lymphocytes as a group are resistant cells, stain typically and the non-granular protoplasm gives a sharp "Myelium" reaction" - (i.e. Erythrosin Acet. sod. reaction).... "The large leukoemic lymphocyte certainly differs from lymphocytes in staining properties, it smears so easily that it is a feature of the cell, and the protoplasm, though often a very thin zone, gives a reaction for alkali never intense but resembling that given by the polymorpho nuclears. The protoplasm also stains a very faint pink colour with methylene blue & eosin and a few very fine neutrophile granules may also be seen... The leukoemic leucocyte may probably be regarded as a myelogenic cell of abnormal blood, the feature of the blood in acute, and a constituent of the blood in myelogenous leukoemia."

Such cells - different from the usual large and small lymphocyte of the blood, and similar to myeloblasts, are not only found in leukoemia, but also in pernicious anaemia and in typhoid fever.

In typhoid fever Uskow described certain transparent cells, larger and differing widely morphologically from ordinary lymphocytes. Noegeli⁽⁶⁵⁾ describes these cells in detail, and shews that they are identical in every way with his myeloblasts, and differ from the ordinary lymphocyte. Their staining reaction given in acute leukoemia, pernicious anaemia, and typhoid blood, and by a large number of marrow cells in the same diseases is described as characteristic. The nucleus stains very faintly and no true granulation is shewn with the triacid stain. Stained at 131° C. in pure alcoholic methylene blue, the nucleus of the myeloblast stains deeply, and the cytoplasm considerably lighter, while the reverse takes place in the case of lymphocytes. It is more than probable that these cells, - giving the same reaction in leukoemia, pernicious anaemia and typhoid fever are identical with, or allied to, Benda's "Myelogenien, Ehrlich's, Froenkel's and Pappenheim's 'Large Lymphocyte,' Grawitz's 'unripe cells,' Wolff's indifferent lymphoid cell, Türk's 'Lymphoid marrow cells,' Troje's 'marrow cells,' and Buckmaster's "Large lymphocyte (?)"

A Mds cell Leucocytosis, which is not always constantly present in leukoemia, has been recorded in a few cases of neoplasm, septic bone diseases, skin diseases, and chlorosis. Ehrlich's early observations

on the presence of eosinophile cells in leukoemia, as offering a feature of distinction between the blood changes in infections and in leukoemia, is proved now to be so incorrect, that it need only be mentioned.

It seems therefore that the difference between the blood picture of leukoemia and that of infective diseases, is not to be found in Muir's full statement made in 1893. But if we accept Noegeli's work, we must acknowledge that the difference is neither one of quality of cells, nor one of quantity, but one in the relative increase of certain types of cells, - this difference then becomes one of degree only. Unfortunately we have not sufficient evidence to form a comparison between an early leukoemia and an ordinary leukoemia. I have had the good fortune to observe the blood changes in one case, and am of the opinion that in such a stage of the disease there is no difference at all, save perhaps for the presence of a few ^{myelocytes} ~~normoblasts~~ (see p. —). An experience which emphasises the truth of Von Lembeck's ⁽⁶⁶⁾ statements:-

"The differential diagnosis from other diseases is often difficult in all forms of leukoemia, in many cases a microscopic examination is sufficient, but there are cases in which the distinction from pathologic leucocytosis is doubtful. Formerly the relative proportion of white and red corpuscles was thought to

be a decisive point, e.g. a ratio of one to fifty or one or twenty was said to be diagnostic of leukoemia. Such, might, however exist in a case of intense leucocytosis especially in an anaemic individual. A numerical criteria too, does not indicate any difference in pathological process. Other infallible criteria were sought for, especially after the development of Ehrlich's criteria - the apparent increase of eosinophile cells - does not always hold good and the reliability of the diagnostic sign more recently proposed by Müller, viz. the presence of marrow cells, has been of late questioned. Hence it appears there is no one certain diagnostic sign of leukoemia.

In making a diagnosis, the most important point is the preponderance of mononeuclear cells and next to this the appearance of marrow cells, etc."

During the clinical course of a leukoemia we may also observe certain changes in the blood picture, which are comparable to those found in infective diseases. Three kinds of factors seem to be responsible for a diminution in the number of leukocytes which is usually associated with a partial involution of the diseased organs.

Superadded infection according to Cabot (l.c.) may cause no effect on the leucocyte count, or a genuine leucocytosis with or without a diminution of the leukoemia.

Therapeutic influences, such as medicinal and X-ray treatment, have a marked effect sometimes in diminishing, and temporarily abating, the disease. There are in addition irregular intermissions in the leukoemia, and constitutional symptoms, which are more or less marked in different cases, and which seem to be dependent on ^{nothing but} a characteristic of the disease itself.

Again Forbes and Longmead (l.c.) referring to acute cases, have shewn that a fatal issue, even without an intercurrent infection, is practically always associated with a marked decrease in leucocytes. Apparently this is not always the case, for Van Lembeck (l.c.), referring to the acute cases compiled by Ebstein and Kossler, remarks that "A large degree of leucocytosis was invariably obtained, but sometimes it appeared only just before death." Such 'terminal' leucocytic increase or diminution is comparable with the so called 'Agonic' leucocytosis or leucopoenia that occurs in infective diseases. Buckmaster's examinations of the blood in one case of spleno-medullary leukoemia "shewed how the blood may alter from week to week, but what is more remarkable, as this case developed, the blood became normal during the fortnight before death.

The myelocytes and mast cells entirely disappeared, a very large number of specimens conclusively

established this fact. Indeed from the blood examination at this stage of the disease it was impossible to state any pathological change." Such a case is apparently one in which the normal intermissions were markedly present - two such intermissions were noticed to occur in six months. Osler (l.c.) states "In another of our cases the blood became normal and the spleen tumour disappeared twice in one year. Altogether I have seen four cases in which the leucocyte count became normal, in three the splenic enlargement persisted." This periodicity is a most important point in the study of leukoemia. Such an occurrence has not to my knowledge any equal in the study of 'new growth' formation.

That every other change occurs in the manner of new growth formation, and that similar changes occur in the leucocyte count in infective diseases, are well established facts, which do not warrant the arrest of speculation by comparing a diminution in the blood count in leukoemias which have become infected, to the action of Colley's fluid in sarcoma, or suppuration in a rodent ulcer, nor by considering these characteristic intermissions - when they present themselves in a less marked degree and more frequently - to be the same as those observed in malignant disease. It is quite illogical to attempt such a

comparison. For to make any accurate comparison we must firstly possess a complete analysis of our standard, - we know something of the probable explanation of the changes in infective diseases, and can not even attempt an explanation in the case of malignant disease;- secondly we must realise the truth that the more incomplete the analysis of our standard, the less we have to find the differences in the process of comparison, and the more we must limit our method to the finding of analogies.

We know then that such intermissions do occur in nearly every subacute infectious disease, ^{-where we can explain them,-} a good example of which we have in subacute tubercular leprosy, and we also have a possibly similar mechanism to that caused by an intercurrent infection resulting in the partial disappearance of the leukoemic blood picture in Metchnikoff's experiments quoted by Ehrlich⁽⁶⁷⁾ as "he was immunising a rabbit with spermatozoa and noticed that in consequence of a purulent process which developed during the course of immunisation, the complement which activated the spermatotoxin disappeared from the serum.....

These isolated observations seem to indicate that the complements can disappear during pathological conditions in consequence, perhaps, of a more rapid destruction, or of a slower formation."

It is theoretically possible, that leukoemia is the reaction of the body seeking to establish immunity, and requiring the action of amboceptors and complement. It will be seen that such a progressive condition would involve the using up of a considerable quantity of idio-complement, and more effectively - tending towards "its rapid destruction" or a production too slow to meet its demands, and that an inter-current infection would be potent enough to deflect the complement. Such an occurrence would cause a complete paralysis of the bone marrow to the leukoemic stimulus, for it would be useless to continue a proliferation which would be quite ineffective without complement.

To parenthesise, and shortly return to the subject discussed above, regarding the improbability of a 'status intoxicus', I am aware that Metalnikoff⁽⁶⁸⁾ obtained an auto-spermatoxin, by immunising guinea-pigs against guinea-pigs' spermatozoa, and that such an anti-body, while capable of killing spermatozoa 'in vitro', were not directed against these spermatozoa 'in corpore'. This, according to his explanation, is due to the fact that the macrocytase (complement) is only present in the leucocytes, and in the serum, after phagolysis, or injury to these cells had occurred - as in obtaining the serum etc., or in injecting spermatozoa interperitoneally; and that the anti-body or

fixative was both 'fixed' to the spermatozoa, and free in the serum. Ehrlich, (l.c.) who will not regard the leucocyte as the only source of complements, agrees with the general outlines of the above explanation, and remarks, "But such an injurious action on the spermatozoa does not take place; even in the slightest degree, in the living animal because as Metelnikoff's researches shew, only the immune body combines with the spermatozoa; not the complement. In this case therefore an antitoxin within our meaning, one that destroys the cells of its own body, does not exist." It is to be noticed that such experiments and explanations have only a bearing on the behaviour of the complement, and not any serious influence on the subject of auto-intoxication; for it is to be remembered that spermatozoa are in reality cells which, when they are freed in the tubules, have undergone both vital and nuclear changes, and acquired an independent life and existence of their own, and most probably differ in molecular construction from the other cells of the same organism. Hence in this case it is possible that a true auto-cytotoxin has not been developed, but an 'iso'-cytotoxin. Therefore, as Ehrlich says, such an antitoxin does not exist, and cannot be demonstrated experimentally, and no genuine evidence of one can be given; while on the other hand, the number of iso-toxins, which may be obtained

experimentally, is legion. This is the most important point which demands our attention to prevent errors in the study of natural immunity.

To return to the subject of leukoemia and infective diseases - what are the causes of difference in the type of leukocytosis in infective diseases? There is no evidence that toxins or poisons have any special selection in the kind of leukocyte called forth. All poisons seem to cause an ordinary leukocytosis - according to Von Jaksch, the action of pilocarpine given subcutaneously is to cause a lymphocytosis, while other drugs etc., cause a leucocytosis. It is more than probable therefore that the anatomical site of development of the toxin, or the site of the tissue, causes a difference in the selection in type of leucocytes. Thayer drew attention to this on the grounds that typhoid bacilli infections of the alimentary canal, even in relapses, was responsible for a lymphocytosis, while a pure typhoidal infection elsewhere, e.g. (empyaema) caused a polymorpho nuclear leucocytosis. This has been my experience in one case of post-typhoidal empyaema showing no other infection on cultivation. In abdominal influenza the absence of an ordinary leucocytosis is also said to occur. I am inclined to believe that in such infections which specially attack the lymphatic tissues - as septic tonsillitis, diphtheria, malaria etc., - a mixed leucocytosis (i.e. a few myelocytes an ordinary leucocytosis

is more liable to occur. Froenkel⁽⁶⁹⁾ has found myelocytes in the enlarged glands of a case of scarlet fever. In a case of empyema, which, after operation, became infected with a fatal fulminating diphtheritic infection, I found the blood count shewed a pure leucocytosis. It is usual in pharyngeal of such severity to find from 5-12% myelocytes. If we do not accept the theory, that any one variety of leucocyte is called for by a particular toxine, we must, for the present at least, adopt Thayer's hypothesis to explain the widely different blood pictures, which characterise certain specific infections.

The presence of normoblasts and megaloblasts in leukoemic bloods is also of considerable theoretical importance. Scott (l.c.) explains this well known fact in myeloid leukoemia, by adopting Ehrlich's view, and considering their presence as part of the disease itself, on the well established fact that "they are met with in the blood when the red cells and haemoglobin are undiminished or even above normal." Scott continues "on the other hand in lymphanoid leukoemia they are generally scarce but may occur in the blood even when the red cells are undiminished.... It is not necessary to regard their formation as a leukoemic stimulus, but rather as a response to physiological needs." Hirschfeld's and Poppenheim's explanation of the occurrence of myelocytes and normoblasts, as due to irritation, is also quoted. These authors compare this to a

hypothetical irritation, which is supposed to bring about the same changes in tumours involving medullary tissue. Such a hypothesis must be abandoned. We do know that a toxin is present in tumours, (Grawitz - 70) and that an injection of tumour extract causes leucocytosis etc. We have ample clinical proof that this does not only happen experimentally, for leucocytosis actually occurs during the course of a case of cancer, and presumably associated with the absorption of such toxins contained within the tumour (theoretically they may or may not be developed as the result of tumour formation). Moreover certain unknown toxins are probably responsible for the considerable anaemia and cachexia in advanced cases, even when the blood forming organs are not involved in tumour formation. Although Kullman⁽⁷¹⁾ and Macheli⁽⁷²⁾ and Donati and others have found haemolytic substances in tumour extracts, it is to be remembered that, as such substances are soluble in alcohol, coctostable, not complex in structure, not specific in any way, and that no anti-bodies are formed towards them, they are therefore similar to those found as a common constituent of all organ extracts by Korschun and Morgenroth⁽⁷³⁾, and cannot therefore be considered of ^{any} ~~much~~ importance. Schwalbe⁽⁷⁴⁾ demonstrated iron granules in cancer cells, occurring independently of haemorrhages, and Tracy⁽⁷⁵⁾ on the other hand did not find any iron in tumours other than that associated with

haemorrhages, and the building up of the tumour mass itself. Whatever may be the explanation of such findings, we can only be certain on one point, that iron is required for the building up of the tumour mass; we can neither say that no active haemolytic substance exists in tumours, nor can we prove its existence. Further, as far as we know, any such haemolytic substance may give rise to a marrow reaction, and cause the production of erythroblasts. On these uncertainties it seems that Hirschfeld's and Poppenheim's comparison is ill chosen. It is surprising that Poppenheim considers the anaemia in leukomia to be due to haemolysis in part, and yet prefers to attribute the presence of erythroblasts to irritation. That haemolysis, does occur in leukoemia to an appreciable extent, is an established fact. We find that in leukoemia, the red cells are specially liable to succumb to haemolytic agents (Peyton Rous)⁽⁷⁶⁾, that they often shew basophilic granulation, and that iron pigmentation is of frequent occurrence in the liver, spleen, marrow etc.

In Scott's hypothesis, that the change in type of cell in leukoemia is due to the leukoemic noxae acting on cells which are capable of developing into more mature forms, and caused so to do, in a manner in which at one time certain varieties of their descendants predominate, we have an explanation of the presence of erythrocytes in myeloid leukoemia, and their relative absence in lymphatic leukoemia. We have

moreover, in this hypothesis, certain other considerations that will, I believe, help our study, though necessarily complicate it. We can assume, correctly, I believe, that we cannot define sharply between the causes of free erythroblasts in either type of the disease, and that in both types their presence is due, to some extent, to a response on the part of the organism to the blood destruction, which is present, even in the early stages of the disease; but that in the myelogenous type, this may be further augmented by the causative noxae, or stimuli of the disease, constituting then the condition known as leukanaemia, more commonly found in relation to myelogenous leukaemia, and being responsible for the appearance of the blood picture of a more or less megaloblastic type.

This group of cases then consist of those shewing either a combined megaloblastic and myeloblastic (large leukaemia lymphocytes, megaloblasts and myelocytes) blood, or a megaloblastic blood at one time, and myeloblastic at another.

(76) (77)
Litten and Gottlieb reported cases which shewed first a leukaemic blood, and later the blood picture resembling a megaloblastic anaemia of Biermer's type.

(85) (86) (80) (81)
Von Leube, Von Leube and Arneith Luce, Weber,
(82) (83)
Drysedale, Hurter, and Buchanan (l. c.) describe cases in which the blood was megaloblastic, and resembled that of a case of pernicious anaemia of Biermer type, and later became typically leukaemic. These authors

consider such abnormal types to be true myeloid leukoemias. Luce however, believes such a blood picture to be common to a variety of conditions - injuries, haemorrhages, intoxications, infections, malaria, malignant disease etc. In most cases the count is lower than in ordinary leukoemia, neutrophilic myelocytes having predominated in some, large or small lymphocytes in others during their leukoemic phases, eosinophile cells on the other hand being absent. That we can class such cases as cases of true leukoemia, is not to be doubted. The blood picture of a true leukoemia may be very closely imitated by any of the above conditions enumerated by Luce, in the same way that they might present leukanaemic features. There is therefore no necessity to make this separation.

It is theoretically correct to regard this change in type of blood picture as analogous to that which occurs in leukoemia, and to apply Scott's hypothesis, with modifications, as an interpretation of their change. In leukanaemia, during the time the blood picture is megaloblastic, for some unknown reason, the leukoemic noxae, acting on the myeloblasts, expend themselves in causing a proliferation of ^{these} myeloblasts in the direction of a megaloblastic production. Later, for some reason, the leukoemic noxae act on these myeloblasts, and condition them to develop myelocytes and other myeloblasts.

From a cytological aspect, since the megaloblastic metaplasia can occur as the blood features of pernicious or megaloblastic anaemia - considered by Ehrlich and others to be due to a megaloblastic degeneration of the bone marrow, or a retrogression to the foetal type of blood production, and since an identical metaplasia occurs in one phase of a leukanaemia, and that later this metaplasia becomes myeloblastic, and is responsible for the appearance of the leukoemia - also considered to be a myeloblastic degeneration, or a retrogression to the foetal type of leucocyte production, therefore we must realise, that from a cytological aspect at least, both pernicious (megaloblastic) and leukoemia are caused by the same, or allied cytogenic factors, and that leukoanaemia is the connecting link between these two diseases.

Further, a biological study of the cells involved in the two conditions, is quite compatible with this view; in pernicious anaemia these myeloblasts are caused to proliferate into megaloblasts by an unknown stimulus - thus causing a less fruitful type of blood production, and causing these megaloblasts to be hurried through their normal cycle, and perform their apparently useless function, but more rapidly approaching their non-nucleated or passive state (megalocytes) in which no further development or generation is possible, and in which they are accordingly destroyed.

In leukoemia, the same thing happens, but for some unknown reason, this proliferation is modified, or altered, in direction, the myeloblasts being now caused to proliferate into other myeloblasts and myelocytes - cells which again, being hurried through their cycle, undergo more rapid proliferation, emigrate into the perivascular and connective tissues, and accumulate there, giving rise to leukoemic infiltrations which may be almost indistinguishable from tumours, and are capable of doing so because it is not in their cycle to become passive, but to remain ~~in~~ active nucleated cells, capable of further division until eventually leucocytolysis ends their cycle of existence. From this we would be lead to assume that the difference in the one type of cell, of becoming 'passive', and in the other, of remaining 'active' and nucleated, consists of a difference in the sense that in pernicious anaemia, proliferation is sufficient to meet the destruction, and in leukoemia destruction is insufficient to meet proliferation; in the first, there is therefore a total diminution, in the second, a total increase in the cellular elements of the blood.

It is my belief that this destruction is both haemolytic and leucolytic in both diseases, but that in pernicious anaemia, the haemolytic element is increased, while in leukoemia, leucolysis predominates, and that in both cases, the destructive changes are

not an exaggeration of the normal changes, but due to some unknown cause, and constitute the so-called 'noxoe,' or 'stimuli', which indirectly condition this cell proliferation.

If this cytological conclusion, in spite of its solid foundation, cannot be accepted because of other stronger contradictory evidence, then we can pronounce the cytogenic and biological doctrines by themselves as being useless, both in the nosological, and aetiological study of the disease.

As a matter of fact pernicious anaemia, according to Hunter's description of the disease, seems to have many clinical points - in fact I may say the chief clinical points - in common with leukoemia. He does not however accept either Ehrlich's or Biermer's identification of the disease, and considers their statements "as an interesting pathological generalization.....that anaemias may be divided into two classes, the normoblastic, and megaloblastic.

It is even a still bolder, and more fascinating clinical generalization, to identify these two groups with the clinical groups of simple, and pernicious anaemia respectively, ⁽⁷⁸⁾ " He does however allow the frequent occurrence of megaloblasts in Addison's anaemia as well as in other anaemias, and regards that "the change can be induced experimentally in a few days by injection of haemolytic agents". "The marrow responds

in this emergency with nucleated red cells of normoblastic or megaloblastic type, depending upon the extent of their destruction "(Bunting 1907)" (p. 176.)

I have myself, on two occasions, been tempted to make the diagnosis of pernicious anaemia, on the marked presence of megaloblasts in patients, who were suffering undoubtedly, as the subsequent clinical aspect proved, from simple chlorosis. Hunter's opinion of cytological Criteria in the study of anaemia, is aptly considered as follows, "To assert that megaloblastic degeneration of the bone marrow is the essential cause of Addisonian anaemia or any other anaemia is just as correct as to say that "normoblastic degeneration" is the essential cause of all other anaemias in which it is found..... or that myelocytic degeneration is the essential cause of splenomedullary leukaemia,"

He defines Addisonian anaemia as a specific infective disease, characterized by the mode of onset, clinical features and course, and having a definite double aetiology in a septic infection, and a specific haemolytic infection, showing post-mortem infective, and haemolytic lesions, and a hyperplastic marrow. The mode of onset etc. he describes in p. 117, "The two important points to which the author would like to draw attention are:- (1) That the glossitic changes are of varying intensity in different cases... (2) that they are closely similar to those met with in the mucosa of the stomach and less commonly of the intestine."

"The clinical observations have been made in seventy five marked cases of Addisonian anaemia which have been under my care during the past seven years. I have made a close study of the glossitis presented by every one of these cases without exception and never observed in other condition - its mode of onset, its appearance, and above all its periodicity." Hunter considers these lesions of great aetiological significance in Addisonian anaemia.

That oral, and gastro-intestinal infection, seem to have the same significance in the production of leukoemia as has been mentioned above.

Again Hunter (p.116) remarks on the characteristic periodicity or intermission, in Addisonian anaemia. In leukoemia the same tendency, though to a less marked degree, has been said to occur. The progressive nature of both diseases is well known.

From a pathological aspect, (p.111) he draws attention to the 'haemolytic lesions', i.e. pigmentation of the liver, and other organs, with iron granules. In leukoemia this pigmentation, although to a less degree, has the same distribution, and chemical reaction, (~~vide infra~~) as mentioned above and in (p.155) he regards the marrow changes as toxic and infective and disagrees with the idea of embryonic metaplasia on experimental and other evidence. In leukoemia the marrow changes are a so called myeloblastic metaplasia, such as may occur in typhoid (Naegali l.c.) We have further haematological analogies in the two diseases - it has been shewn that in

leukoemia, the blood picture of pernicious anaemia may be imitated; it is also an established fact, that in pernicious anaemia, the marrow may suddenly react, in a way to cause a blood state of leukoemia.

Cabot (l.c.) reports a case of pure pernicious anaemia which, soon before death, shewed a blood picture of a typical small celled leukoemia.

Buckmaster (l.c. p.176) mentions the enormous myelocytosis which may occur in an acute phase of pernicious anaemia, even as to be a course of error in diagnosing 'acute myeloemia'. We know that the "leukoemic lymphocyte", according to Naegali, (l.c.) and myelocytes, occur frequently, though in small numbers, in ordinary cases of pernicious anaemia.

(78)

Cabot is of the opinion that these two diseases are intimately related, especially in children:-

"It seems to me the most natural conclusion to be deduced from these facts is that we meet with cases in infancy which are apparently intermediate between leukoemia and pernicious anaemia." The facts he refers

to, which lead him to this conclusion, are apparently those cases of fatal anaemia in children, which shew certain blood changes common to both diseases.

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Cohnhein discussing the nature of anaemia in leukoemia, comes to the same conclusion.

"But pari passu with the increase of white blood corpuscles there occurs as we have emphatically stated,

an equally marked increase in red ones, and here the same difficulties crop up as in the other forms of essential anaemia formerly considered. That this is not a mere superficial analogy is indicated with unmistakable clearness by the course of those remarkable cases in which a pure essential anaemia has preceded the leukoemia for a longer or shorter period.

Litten has seen a case in a woman suffering from pernicious anaemia, a typical severe leukoemia developed acutely in a few days. In one of the cases described by Fleischer and Penzoldt, the patient, before becoming leukoemic presented for a considerable time the picture of an exquisite pseudo-leukoemia.

Moreover, instances are not uncommon where the physician has long been obliged to hesitate whether to classify an affection with the chronic anaemias or with leukoemia; such cases are to some extent intermediate in nature.

Surely, then, there is no dearth of close relationship between leukoemia and the remaining so-called essential anaemias; but who would venture at present an exact formentation of these relationships?"

Both Cohnheim and Cabot make these statements on the analogy between pernicious anaemia (or essential anaemia) and leukoemia, apparently solely on the occurrence of "intermediate" cases, and on the case recorded by Litten, which, together with the case of Cabot quoted

above, might have been cases of true pernicious anaemia, shewing an exaggeration of the usual terminal lymphocytosis which occurs in most cases of pernicious anaemia. It is noteworthy that Forbes and Longmead (l.c.) also shew the occurrence of a similar lymphocytosis in acute leukoemias.

Cabot and Cohnheim have omitted to compare the other features which I have enumerated above, and which to my mind more than suggest this analogy between the two diseases. I do not for a moment believe that the two diseases depend on similar causes, but that the cytological changes are similar, and that the causes exciting these changes, are closely related in the two diseases. This analogy must, however, in the meantime remain only a working hypothesis, and its proof or disproof will only be established by an exact knowledge of the causative factors which condition those haematic dyscrasias.

It is also of interest to note that the colour index in leukoemia is sometimes normal, or above normal. Forbes' and Longmead's series of twelve cases shewed five with a high colour index. Scott (l.c. p. 1350) also draws attention to this occurrence. Further Forbes and Longmead have, in their cellular investigations, isolated a streptococcus of the salivarius group from their cases; they are of the opinion that

this organism may not be the primary cause of the disease, but that it is responsible for certain clinical and pathological changes in the disease.

Hunter also centres his attention on a similar organism, as contributing to, if not causing the pathological changes in pernicious anaemia.

It is my opinion that such organisms are capable of modifying the clinical features of these diseases, but that they do not constitute the leukoemic or anaemic 'noxoe.'

The outcome of this is ^{that} ~~but~~ a study from aetiological, clinical, and nosological standpoints of leukoemic diseases, while not proving the infectivity of these diseases, strongly dictates further research in favour of the parasitic or toxic theory, and that the cytogenic doctrine, while offering no disproof whatever towards the infective theory, is absolutely incapable by itself of giving us the solution to one of the most difficult problems in the study of disease. This solution, when found, may also enlighten our views on the origin of tumour formation, and, for this reason, seems of the greatest importance.

It is possible that leukoemic diseases are a stepping stone in the classification and evolution of disease, between the infective granulomata, on the one hand, and neoplasms on the other.

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